PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCA-Ost-118A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50274	International filing date *(day/month/year)* 27.06.2003	Priority date *(day/month/year)* 28.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/395		
Applicant VLAAMS INTERUNIV.INST.VOOR BIOTECHNOLOGY VZW et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.01.2004	20.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50274

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 5-8 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 5,6 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8
	No:	Claims	1-7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 5 and 6 relate to the use of products defined by reference to a desirable characteristic or property, namely the administration of VEGFR-1/PIGF signaling pathway modulator in amounts effective to suppress bone resorption or osteoporosis. The claims cover any modulator of VEGFR-1/PIGF signaling pathway, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the antagonists of PIGF have been searched e.g those mentionned in the examples at pages 19 to 23.

Consequently only the subject-matter of the claims that was searched will be examined as far as novelty, inventive step and industrial applicability are concerned (Rule 66.1(e) PCT).

Claims 5-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01 85796 A (VLAAMS INTERUNIVERSITAIR INST ;COLLEN DESIRE (BE); CARMELIET PETER) 15 November 2001 (2001-11-15)

D2: US-B1-6 369 204 (HORTON MICHAEL A ET AL) 9 April 2002 (2002-04-09)

D3: NIIDA SHUMPEI ET AL: "Vascular endothelial growth factor can substitute for macrophage colony-stimulating factor in the support of osteoclastic bone resorption" JOURNAL OF EXPERIMENTAL MEDICINE, vol. 190, no. 2, 19 July 1999 (1999-07-19), pages 293-298, XP002258707 ISSN: 0022-1007

D4: US 2002/009750 A1 (ROCKWELL PATRICIA ET AL) 24 January 2002 (2002-01-24)

D1 discloses the therapeutical use of PIGF inhibitors such as anti-PIGF antibodies for treating angiogenesis and bone and cartilage destruction (p.3, l.23 to p.4, l.2 ; p.9, l.16 to l.20 ; p.12, l.15 to l.21 and p.25, l.18 to p.29, l.6, claims 1-11).

D2 discloses the therapeutical interest of using a monoclonal antibody against integrin alphaV beta 3 which binds to osteoclasts for treating disorders associated with excessive bone resorption (column 3, l.1 to l.26 and example 7).

D3 discloses that VEGF induces osteoclast recruitment through VEGFR-1 and that VEGF supports the bone resorbing function of osteoclasts (p.294, left-hand column, l.8 to l.15 ; p.294, right-hand column, l.40 to l.57).

D4 discloses the neutralizing anti-VEGFR-1 antibody DC101 and its use for inhibiting angiogenesis and tumor growth (examples 5 and 7).

NOVELTY

The subject-matter of the claims 1-8 is the therapeutical use of PIGF antagonists for treating disorders of bone resorption and osteoporosis. Document D1 discloses therapeutical use of PIGF inhibitors such as anti-PIGF antibodies for treating bone destruction (see passages above). The subject-matter of claims 1-7 is therefore not new (Article 33(2) PCT).

INVENTIVE STEP

Document D2, which is considered to represent the most relevant state of the art, discloses (cf. above) the use of antibody binding osteoclast integrin receptor and having an effect on osteoclast inactivation for treating excessive bone resorption from which the subject-matter of claim 8 differs in that it relates to the therapeutical use of a VEGFR-1 inhibitor.

The effect of the difference is the implication of VEGFR-1 in osteoclastic bone resorption. The problem to be solved by the present invention may therefore be regarded as providing an alternative treatment of osteoporosis and bone resorption by inactivating osteoclasts. The solution proposed in claim 8 i.e. the use of a VEGFR-1 inhibitor solves the problem posed.

Document D3 discloses that VEGF induces osteoclast recruitment through VEGFR-1 and that VEGF supports the bone resorbing function of osteoclasts. Although D3 does not disclose anti-VEGFR-1 antibodies, D3 proposes the use of antibody anti-VEGF to inhibit osteoclasts. It is therefor obvious for a skilled person, starting from D2 and trying to solve the problem posed to combine the teaching of D3 to D2 thus inhibiting the action of VEGF receptor on osteoclasts. It is considered that inhibiting VEGFR-1 or VEGF is equivalent and direcly obvious when it is known that VEGF acts through the VEGFR-1. This is supported by document D4 which discloses the therapeutical use of anti-VEGFR-1 antibody for the treatment of angiogenesis and of tumor growth, which are also stimulated by VEGF through its VEGFR-1 receptor. The subject-matter of claim 8 dealing with a VEGFR-1 inhibitor does therefore not involve an inventive step (Article 33(3) PCT). Among VEGFR-1 inhibitors antibody anti-VEGFR-1 are cited in the description. The same reasoning applies with antibodies anti-VEGFR-1.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 5-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound

in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

CLARITY

The terms "antagonists" and "disorders of bone resorption" used in claims 1 and 3 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). Even with the list stated in claim 3 it is not clear what products could act as PIGF antagonists.

Claims 1 and 5 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.